

Special Article - Epilepsy and Seizure Disorders

Epilepsy and Intracranial Vascular Malformations, a Possible Missing Link!

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Abstract

The development of brain arteriovenous malformations (AVMs) remains enigmatic. Their usual presentation with hemorrhage could be a devastating event. Their second mode of presentation; Seizure poses a mechanistic, diagnostic and therapeutic challenge. For the most part, vascular development and flow abnormalities are implicated in the development of seizures in the context of brain AVMs. Proposed is a hypothesis in which common cortical and vascular development pathways lead to perturbation of the vascular phenotype resulting in arteriovenous shunting while simultaneously leading to focal form of cortical dysplasia conducive of seizure.

Keywords: Intracranial vascular malformation; Epilepsy; Seizure disorders; Cortical development; Cortical dysplasia

Introduction

Cerebral cavernous malformations (CCMs) and arteriovenous malformations (AVMs) represent the major part of the spectrum of intracranial vascular malformations (IVM) [1]. They represent a common source of hemorrhage in young adults, which are the most common cause of intracerebral hemorrhage (ICH) in young adults that often heralded by an epileptic seizure at presentation to medical attention [2,3]. IVM can cause without an intracerebral hemorrhage, representing the second devastating manifestation of IVMs occurring in 15% of all AVM patients [4]. In addition, many of these AVMs and CCM lead to what is known as “non-hemorrhagic focal neurological deficits” for which many possible pathophysiologic mechanisms have been proposed, including inflammatory process and cerebral autoregulatory failure around IVMs [5,6]. This could be as severe and devastating as migraine headaches and Todd’s paresis and at times could be indistinguishable from a seizure event [7].

IVM development is poorly understood, and a number of them are discovered in the course of the workup of another neurologic condition or complaint or if the health system is organized, screening of families of a known affected patient. The prevalence of these lesions is reported around 1:625 for CCM and 1:2000 for AVM [8,9]. This represents a large pool of potential patients with refractory seizures in the population. But on the other hand, due to the poorly understood disease process and the limited number compared to other disease conditions, there is a significant debate as to the trigger for treatment of an uneventful incidental AVM [10]. In a patient presenting with seizures in the context of an AVM, the identification of a hemorrhagic event is discernible by imaging but the debate would still exist whether this is enough to change course and alter the treatment attitude. The dichotomy of seizure manifestation is whether they are clinically overt or subclinical in nature detected only during electroencephalography. These factors would complicate the definition as to which seizure, i.e., clinical or electrographic, for example, would be considered a trigger for treatment.

For seizures specifically, several mechanisms have been proposed in association with IVMs including neuron loss, glial proliferation, derangement of neurotransmitters, and free radical formation [11]. For this particular reason, one of the attitudes taken toward IVMs with seizures is surgical resection to reduce the seizure tendency via secondary epileptogenesis [12] triggering a huge debate with the outcome of recent work questioning a beneficial role of surgery on occurrence or the recurrence of seizure. This compounded with the variety of surgical solutions in tackling the “epileptogenic scars” that are to date never been randomized to allow identifying the most efficient method to reduce the seizure risk after resection of IVMs.

But, What if we are looking at the wrong target?

Hypothesis and Evidence

Several developmental studies for AVM implicate genetic derangements as those in the tumor necrosis factors, tumor growth factors, inter-leukins, vascular endothelial growth and many others in the formation, or should we say malformation of AVM’s development of AVM’s [13]. Recent evidence implicates genes of the Notch signaling pathway in the development of AVM’s [14]. As these genes might be involved in some aspect of the derangement of arterial differentiation and venous regression leading to the formation of the nidus with direct arterio-venous shunting; their mutations are well known to perturb cortical development.

In a simplistic view of situation, the classical description of an AVM is that of a triangular malformation stemming from the ventricular surface with a draining vein either toward the superficial or deep venous outflow. This is, for the most part, reminiscent of the column of theory of cortical development [15]. The latter suggests that each and every segment of the ventricular zone is responsible for populating a column of cortex with neural and glial elements. One can intuitively assume that the same patterning is possible in the vascular elements.

Implication and Discussion

Since both neural and vascular developmental processes are guided, in part; by sets of common and shared genetic pathways, it is fair to assume that the derangement of the one genetic pathway could lead to the development of the AVM and a focal cortical malformation associated with it exclusive to that particular “cortico-vascular” column. Thus, the development of seizure could be attributed clinico-pathologically to an underlying cortical dysplasia or malformation rather than a vascular mal-development or blood flow abnormality. Parallels of this multi-lineage derangement exist in the literature [16,17].

This hypothesis would be easily testable if we analyze the brain tissue around the AVM. Unfortunately, IVM surgery is one of the most refined in micro-neurosurgery, in which the brain around the IVM is respected. It must minimally manipulated, leaving the underlying and surrounding brain out of reach to our scientific inquiry. This would be even more interesting if this particular part of the brain is “eloquent”, with a great potential to be able to shed some light on the adaptive mechanism the developing brain utilizes while facing a hostile lesion like an AVM. May be in autopsies we can find the answer. An answer that would probably refine our understanding of cortical-vascular genetic interaction in relation to epileptogenic AVM's. A change in our understanding of these mechanisms would enable physicians to employ alternate or even novel treatment plans for epilepsy in AVMs. Such strategy would mean a specific regimen is designated to each individual patient based on a genetic recipe of his or her own making. This individualized treatment approach could result in better seizure control without resorting to the controversial surgical excision of the AVM to reduce the seizure tendency and avoid all together the risk of secondary epileptogenesis due to persistent AVM presence or surgical scarring.

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